---

**Article:**
Shimizu, Seishi orcid.org/0000-0002-7853-1683 and Matubayasi, Nobuyuki (2018) A unified perspective on preferential solvation and adsorption based on inhomogeneous solvation theory. Physica A: Statistical Mechanics and its Applications. pp. 1988-1996. ISSN 0378-4371

https://doi.org/10.1016/j.physa.2017.11.113

---

# A unified perspective on preferential solvation and adsorption based on inhomogeneous solvation theory

*Seishi Shimizu*[1,*] *and Nobuyuki Matubayasi*[2,3]

[1]York Structural Biology Laboratory, Department of Chemistry, University of York, Heslington, York YO10 5DD, United Kingdom

Tel: +44 1904 328281, Fax: +44 1904 328281, Email: seishi.shimizu@york.ac.uk

[2]Division of Chemical Engineering, Graduate School of Engineering Science, Osaka University, Toyonaka, Osaka 560-8531, Japan

[3]Elements Strategy Initiative for Catalysts and Batteries, Kyoto University, Katsura, Kyoto 615-8520, Japan

**ABSTRACT**

How cosolvents affects solvation has been revealed through the independent determination of solute-solvent and solute-cosolvent interactions guaranteed by the phase rule. Based on the first principles of inhomogeneous solvation theory, we present here a general matrix theory encompassing both preferential solvation and surface adsorption. The central role of the stability

conditions that determine how many excess numbers (surface excesses) are independently determinable, have been clarified from the first principles. The advantage of the inhomogeneous approach has been demonstrated to be in its ease in treating solvation and adsorption in a unified manner, while its disadvantage, for example in membrane dialysis experiments, can be overcome by the inhomogeneous-homogeneous conversion.

## 1. Introduction

Controlling solvation often requires the addition of a third component (referred to as "cosolvents" throughout this paper) [1–6], which has a number of synonyms (such as denaturants, stabilizers, chaotropes, kosmotropes, hydrotropes, crowders, osmolytes, cosolutes or cosolvents) [7–11]. Even though cosolvents have provided practical solutions to controlling solubility and macromolecular stability, how they actually work has been the source of controversies [12–16].

What is powerful and at the same time confusing about the cosolvent action is the formal analogy between solvation and adsorption [13,16]. The cosolvent-induced modulation of the solvation free energy is understood in terms of the preferential solvation, i.e., the competition between the excess numbers of water and cosolvent in a mathematically identical manner [13,16] to the description of cosolvent modulation of surface tension in terms of surface excesses of water and cosolvent [17–22]. In both cases, the modulation of free energy is explained by the two unknowns (excess numbers or surface excesses of water and cosolvent) [12,13,15,16,23]. The problem here is that the two unknowns cannot be determined from a single measurable quantity [12,13,15,16,23]. In the case of surface adsorption, the Gibbs dividing surface has been introduced to circumvent this

problem [10,13,15,24]. By appropriately positioning the dividing surface, the surface excess of water can be made zero, hence the cosolvent-induced change of surface tension can be attributed entirely to the surface excess of the cosolvent [17–22]. This elegant circumvention of the indeterminate problem, however, has introduced a new, implicit unknown: the precise position of the surface [10,13,15,24].

Due to the formal analogy between adsorption and preferential solvation, the dividing surface approach has been extended to preferential solvation, where the cosolvent-induced change of solvation free energy has been attributed entirely to the excess number of water, when the cosolvents are deemed as being preferentially excluded from biomolecular surfaces [12,13,15,16,23]. This has stirred significant controversy over the molecular-based mechanism of the cosolvent effect [12,13,15,16,23]. We have proposed a resolution for this controversy based on a simple realization that the solvation free energy of a solute should be modulated via two independent variables (cosolvent concentration and pressure) [15] for the determination of two independent quantities (excess numbers of water and cosolvent), which can be achieved by solving simultaneous equations [15]. The existence of such independent variables has been shown to be guaranteed by the Gibbs phase rule, which governs the number of independently-determinable Kirkwood-Buff (KB) integrals [16,24]. However, in contrast to preferential solvation, the phase rule permits one less degree of freedom for the adsorption isotherm, making the independent determination of two excess numbers impossible in principle [16,24]. Despite the mathematical analogy, the Gibbs phase rule distinguishes between adsorption and preferential solvation in terms of the degrees of freedom [16,24].

Such clarifications, in our previous papers [16,24], have been achieved in an ad-hoc manner, starting afresh each time with a set of Gibbs-Duhem equations [25] for different cases. Here we show that a general theoretical framework spanning over preferential solvation and Gibbs adsorption can be constructed on the inhomogeneous solvation theory [26–31] in a unified manner, bringing forth clarity and unity in the elucidation, demonstrating that the stability condition plays the central role on the determinability of independent excess numbers.

Inhomogeneous solvation theory provides an alternative perspective on the study of solvation [26–31]. Unlike the homogeneous solution theory which does not treat the solute in any way distinct from the solvent species, the inhomogeneous solvation theory marks out a solute molecule by fixing its centre-of-mass position so that the structure of solvent in the *vicinity* of the specified solute can be clarified with ease. Such difference in the treatment of the solute leads to the complementary strengths and advantages for homogeneous and inhomogeneous theories [26–31]. However, the fluctuation solution theory, since its inception by Kirkwood and Buff [32] and the subsequent inversion procedures for analyzing experimental data [33–35] have relied chiefly on the homogeneous theory, even though the pioneering link between the KB integrals and experimental data have been provided through an intuitive thermodynamic approach in the spirit of the inhomogeneous approach [36]. This inhomogeneous perspective has led to our statistical thermodynamic foundation of preferential solvation [15,16,37,38] and the solubility enhancement mechanism by hydrotropes [7–9,11,39]. Yet the advantage of the inhomogeneous approach has not been exploited fully due to the lack of a general theoretical formulation. Here we demonstrate that the major advantages of the inhomogeneous perspective is in its capacity to describe preferential solvation and Gibbs adsorption in a unified theoretical framework.

## 2. Inhomogeneous solvation, stability condition, and matrix inversion

Here we construct the fluctuation solution (Kirkwood-Buff) theory from a perspective of the inhomogeneous solvation theory, and show its equivalence to the homogeneous approaches [32–35]. Consider an $n$-component solution consisting of water ($i = 1$) and cosolvent molecules ($i = 2, \dots, n$) molecules. The grand potential $J$ can be expressed in terms of grand partition function $\Xi$ in the following manner [39]:

$$J = -kT \ln \Xi(T, V, \mu_1, \mu_2, \dots, \mu_n) \tag{1}$$

in which the temperature $T$, which is kept constant, will be omitted throughout this section. We consider two systems with and without the solute. When the solute is present, it is fixed at the origin and acts as the source for an external field for the water and cosolvent molecules, and the solution system is inhomogeneous [26–31]. When the solute is absent, the system consists only of water and cosolvents, and is homogeneous [39]. The chemical potential of the solute can be expressed in terms of the grand partition functions in the following manner [39]:

$$\mu_u^* = J_u - J_0 = -kT \ln \frac{\Xi_u(V_u, \mu_1, \mu_2, \dots, \mu_n)}{\Xi_0(V_0, \mu_1, \mu_2, \dots, \mu_n)} \tag{2}$$

where the subscripts $u$ and 0 denote the systems with and without the solute, respectively. Previously, we have presented a full order-of-magnitude argument to show that we can set $V_u = V_0$ at thermodynamic limit [39]. From Eq. (2) follows the Gibbs-Duhem relationship which will be our starting point [39]:

$$-d\mu_u^* = kT\sum_i\left[\frac{\partial\Xi_u(V_u,\mu_1,\mu_2,\ldots,\mu_n)/\partial\mu_i}{\Xi_u(V_u,\mu_1,\mu_2,\ldots,\mu_n)} - \frac{\partial\Xi_0(V_0,\mu_1,\mu_2,\ldots,\mu_n)/\partial\mu_i}{\Xi_0(V_0,\mu_1,\mu_2,\ldots,\mu_n)}\right]d\mu_i = \sum_i\left[\langle N_i\rangle_u - \langle N_i\rangle_0\right]d\mu_i \tag{3}$$

where $V\left[\left(\langle N_i\rangle_u - \langle N_i\rangle_0\right)/\langle N_i\rangle_0\right]$ is the Kirkwood-Buff integral (KBI) between the solute and the *i*-th solvent species [39]. Thus the number difference between solute's vicinity and bulk has been formulated in the framework of the inhomogeneous solvation theory, thereby fulfilling Hall's phenomenological approach, based upon the Gibbs-Duhem equations for the vicinity and bulk regions [36], rigorously from first principles [39].

Now we apply the Gibbs phase rule to this system to enumerate the degrees of freedom [16]. Considering that the external field does not affect the degrees of freedom, an $n$-component system ($C = n$) in one phase ($P = 1$) has $F = C - P + 2 = n - 1 + 2 = n + 1$ degrees of freedom. Under a constant $T$, the system has $n$ degrees of freedom.

Thus the $n$ variables to modulate the solvation free energy can be chosen based on different needs and strategies, such as (a) to match the experimental setup or (b) for the convenience of experimental data analysis. There are a number of possible ways to choose the $n$ variables. The following are some of the most illustrative examples

**(i) Solvent and hydrotrope concentrations, $c_1, \ldots, c_n$,** can be chosen as the $n$ independent variables, which transforms Eq. (3) into the following

$$-\left(\frac{\partial\mu_u^*}{\partial c_\alpha}\right)_{c_{\alpha'\neq\alpha}} = \sum_i\left(\frac{\partial\mu_i}{\partial c_\alpha}\right)_{c_{\alpha'\neq\alpha}}[\langle N_i\rangle_u - \langle N_i\rangle] \tag{4}$$

Note that $\left(\frac{\partial \mu_i}{\partial c_\alpha}\right)_{c_{\alpha' \neq \alpha}}$ is related to a well-known $A$ matrix via $\left(\frac{\partial \mu_i}{\partial c_\alpha}\right)_{c_{\alpha' \neq \alpha}} = RT\, A_{i\alpha}$, and $-\left(\frac{\partial \mu_u^*}{\partial c_\alpha}\right)_{c_{\alpha' \neq \alpha}}$ and $[\langle N_i \rangle_u - \langle N_i \rangle]$ are vectors. Hence the determination of KBIs involves the solution of the simultaneous equations via the calculation of the inverse of $A$ matrix. Note that the stability condition for the single-phase solution mixture requires $|A| > 0$, which guarantees the existence of $A^{-1}$. When there is phase-separation, $A^{-1}$ does not exist, which makes it impossible to determine the KBIs. This is the generalization of our previous discussion on the indeterminate nature of KBIs for surfaces. This particular form of matrix $A$ has been introduced by Kirkwood and Buff [32] and also been used by Ben-Naim [33] and Smith [34,35] for matrix inversion within the framework of the homogeneous solution theory. We have thus confirmed the equivalence between homogeneous and inhomogeneous approach to KBIs under the present choice of independent variables.

**(ii) Chemical potentials, $\boldsymbol{\mu_1}, \ldots, \boldsymbol{\mu_n}$,** can be chosen as the $n$ independent variables, which yields

$$-\left(\frac{\partial \mu_u^*}{\partial \mu_\alpha}\right)_{\mu_{\alpha' \neq \alpha}} = \sum_i \delta_{i\alpha} \left[\langle N_i \rangle_u - \langle N_i \rangle\right] \tag{5}$$

due to $\left(\frac{\partial \mu_i}{\partial \mu_\alpha}\right)_{\mu_{\alpha' \neq \alpha}} = \delta_{i\alpha}$. Hence Eq. (5) reduces to the definition of thermodynamic fluctuation, $-\left(\frac{\partial \mu_u^*}{\partial \mu_\alpha}\right)_{\mu_{\alpha' \neq \alpha}} = [\langle N_\alpha \rangle_u - \langle N_\alpha \rangle]$, which leads back to the statistical thermodynamics of fluctuation both in the framework of inhomogeneous solvation theory [16,39], which has been shown [16,39] to be equivalent to the formalism in homogeneous solutions [32–35]. This example may seem trivial in the current representation (Eq. (5)) of preferential solvation, yet will be shown in Section 3 to be of central importance in the difference between preferential solvation with adsorption isotherm.

**(iii) Semi-permeable membrane transmitting the $n$th component only.** In this case, the independent variables are $\mu_1, \dots, \mu_{n-1}, P$, and $\mu_n$ is dependent on these variables through the Gibbs-Duhem equation as

$$d\mu_n = \frac{1}{c_n}[-\sum_i c_i d\mu_i + dP] \tag{6}$$

Under this constraint, we obtain the following matrix relationship:

$$-\left(\frac{\partial \mu_u^*}{\partial \mu_\alpha}\right)_{\mu_{\alpha' \neq \alpha'}, P} = \sum_i \left(\frac{\partial \mu_i}{\partial \mu_\alpha}\right)_{\mu_{\alpha' \neq \alpha'}, P} [\langle N_i \rangle_u - \langle N_i \rangle] \quad (\alpha = 1, \dots, n-1, \alpha' = 1, \dots, n-1) \tag{7a}$$

$$-\left(\frac{\partial \mu_u^*}{\partial P}\right)_{\mu_{\alpha'}} = \sum_i \left(\frac{\partial \mu_i}{\partial P}\right)_{\mu_{\alpha'}} [\langle N_i \rangle_u - \langle N_i \rangle] \quad (\alpha' = 1, \dots, n-1) \tag{7b}$$

Note that the $n$th row (Eq. (7b)) had to be written down separately from the rest (Eq. (7a)) because it involves pressure instead of chemical potential. Due to the Gibbs-Duhem constraint (Eq. (6)), the matrix elements in Eq. (7) have different expressions and interpretation from (ii). To understand this, let us examine for simplicity the case of $n = 2$, for which the matrix relationship can be expressed as

$$-\begin{pmatrix} \left(\frac{\partial \mu_u^*}{\partial \mu_1}\right)_P \\ \left(\frac{\partial \mu_u^*}{\partial P}\right)_{\mu_1} \end{pmatrix} = \begin{pmatrix} 1 & \left(\frac{\partial \mu_2}{\partial \mu_1}\right)_P \\ 0 & \left(\frac{\partial \mu_2}{\partial P}\right)_{\mu_1} \end{pmatrix} \begin{pmatrix} \langle N_1 \rangle_u - \langle N_1 \rangle \\ \langle N_2 \rangle_u - \langle N_2 \rangle \end{pmatrix} \tag{8}$$

Now the determinant, which plays a key role in the determinability of the two KBIs, can be expressed as

$$\begin{vmatrix} 1 & \left(\frac{\partial \mu_2}{\partial \mu_1}\right)_P \\ 0 & \left(\frac{\partial \mu_2}{\partial P}\right)_{\mu_1} \end{vmatrix} = \left(\frac{\partial \mu_2}{\partial P}\right)_{\mu_1} > 0 \tag{9}$$

The sign of Eq. (9) comes from the osmotic stability condition [40], in which the increase of osmotic pressure should necessarily be accompanied by the increase of the chemical potential of

the species 2 (which cannot pass through the membrane). Phase separation arises when this stability condition is broken. Hence the determinant of the matrix in Eq. (7) should be considered to be an $n$-component generalization of this osmotic stability condition. When the system is in a single phase, the matrix elements can be evaluated using the Gibbs-Duhem equation as

$$\begin{pmatrix} 1 & \left(\frac{\partial \mu_2}{\partial \mu_1}\right)_P \\ 0 & \left(\frac{\partial \mu_2}{\partial P}\right)_{\mu_1} \end{pmatrix} = \begin{pmatrix} 1 & -\frac{c_1}{c_2} \\ 0 & \frac{1}{c_2} \end{pmatrix} \tag{10}$$

whose determinant is always positive due to $c_2 > 0$.

**(iv) Preferential solvation and volumetric experiments** [15,16] forces one to choose the variables in a manner not as straightforward as the previous examples. Let us focus here on the system composed of one dilute solute (external field) in water-cosolvent mixture. What experiments measure are $\left(\frac{\partial \mu_u^*}{\partial \mu_1}\right)_P$ and $\left(\frac{\partial \mu_u^*}{\partial P}\right)_{N_1}$ [15,16]. With the thermodynamic identity,

$$\left(\frac{\partial \mu_u^*}{\partial P}\right)_{N_1} = \left(\frac{\partial \mu_u^*}{\partial P}\right)_{\mu_1} + \left(\frac{\partial \mu_u^*}{\partial \mu_1}\right)_P \left(\frac{\partial \mu_1}{\partial P}\right)_{N_1} \tag{11}$$

we can convert the set of experimental values $\left(\frac{\partial \mu_u^*}{\partial \mu_1}\right)_P$ and $\left(\frac{\partial \mu_u^*}{\partial P}\right)_{N_1}$ to the ones in the case (iii) through the following matrix relationship:

$$\begin{pmatrix} \left(\frac{\partial \mu_u^*}{\partial \mu_1}\right)_P \\ \left(\frac{\partial \mu_u^*}{\partial P}\right)_{\mu_1} \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ -\left(\frac{\partial \mu_1}{\partial P}\right)_{N_1} & 1 \end{pmatrix} \begin{pmatrix} \left(\frac{\partial \mu_u^*}{\partial \mu_1}\right)_P \\ \left(\frac{\partial \mu_u^*}{\partial P}\right)_{N_1} \end{pmatrix} \tag{12}$$

(Note the change in the parameters fixed in the partial differentiation.) Thus the simultaneous equation for the present choice of variables becomes

$$-\begin{pmatrix} \left(\frac{\partial \mu_u^*}{\partial \mu_1}\right)_P \\ \left(\frac{\partial \mu_u^*}{\partial P}\right)_{N_1} \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ -\left(\frac{\partial \mu_1}{\partial P}\right)_{N_1} & 1 \end{pmatrix}^{-1} \begin{pmatrix} 1 & \left(\frac{\partial \mu_2}{\partial \mu_1}\right)_P \\ 0 & \left(\frac{\partial \mu_2}{\partial P}\right)_{\mu_1} \end{pmatrix} \begin{pmatrix} \langle N_1 \rangle_u - \langle N_1 \rangle \\ \langle N_2 \rangle_u - \langle N_2 \rangle \end{pmatrix}$$

$$= \begin{pmatrix} 1 & \left(\frac{\partial \mu_2}{\partial \mu_1}\right)_P \\ \left(\frac{\partial \mu_1}{\partial P}\right)_{N_1} & \left(\frac{\partial \mu_2}{\partial P}\right)_{\mu_1} + \left(\frac{\partial \mu_2}{\partial \mu_1}\right)_P \left(\frac{\partial \mu_1}{\partial P}\right)_{N_1} \end{pmatrix} \begin{pmatrix} \langle N_1 \rangle_u - \langle N_1 \rangle \\ \langle N_2 \rangle_u - \langle N_2 \rangle \end{pmatrix}$$

$$= \begin{pmatrix} 1 & \left(\frac{\partial \mu_2}{\partial \mu_1}\right)_P \\ \left(\frac{\partial \mu_1}{\partial P}\right)_{N_1} & \left(\frac{\partial \mu_2}{\partial P}\right)_{N_1} \end{pmatrix} \begin{pmatrix} \langle N_1 \rangle_u - \langle N_1 \rangle \\ \langle N_2 \rangle_u - \langle N_2 \rangle \end{pmatrix} \quad (13)$$

Note that $\begin{vmatrix} 1 & \left(\frac{\partial \mu_2}{\partial \mu_1}\right)_P \\ \left(\frac{\partial \mu_1}{\partial P}\right)_{N_1} & \left(\frac{\partial \mu_2}{\partial P}\right)_{N_1} \end{vmatrix} = \left(\frac{\partial \mu_2}{\partial P}\right)_{N_1} - \left(\frac{\partial \mu_2}{\partial \mu_1}\right)_P \left(\frac{\partial \mu_1}{\partial P}\right)_{N_1} = \left(\frac{\partial \mu_2}{\partial P}\right)_{\mu_1} > 0$ is the osmotic stability condition. Whether Eq. (13) can be solved for the KBIs depends solely on the osmotic stability condition. This sheds light into why preferential solvation, despite its lack of dividing membranes, have often resorted to the use of hypothetical membranes for interpretation [13,23,24]; the stability condition guaranteeing the KBI determinability is essentially the osmotic stability condition.

When the system can be confirmed to be a single-phase solution, the matrix in Eq. (12) can be evaluated as

$$\begin{pmatrix} 1 & 0 \\ -\left(\frac{\partial \mu_1}{\partial P}\right)_{N_1} & 1 \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ -V_1 & 1 \end{pmatrix} \quad (14)$$

combining Eqs. (10), (13), and (14) yields

$$-\begin{pmatrix} \left(\frac{\partial \mu_u^*}{\partial \mu_1}\right)_P \\ \left(\frac{\partial \mu_u^*}{\partial P}\right)_{N_1} \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ -V_1 & 1 \end{pmatrix}^{-1} \begin{pmatrix} 1 & -\frac{c_1}{c_2} \\ 0 & \frac{1}{c_2} \end{pmatrix} \begin{pmatrix} \langle N_1 \rangle_u - \langle N_1 \rangle \\ \langle N_2 \rangle_u - \langle N_2 \rangle \end{pmatrix} = \begin{pmatrix} 1 & -\frac{c_1}{c_2} \\ V_1 & V_2 \end{pmatrix} \begin{pmatrix} \langle N_1 \rangle_u - \langle N_1 \rangle \\ \langle N_2 \rangle_u - \langle N_2 \rangle \end{pmatrix} \quad (15)$$

where $V_1$ and $V_2$ are the partial molar volumes of species 1 and 2, respectively. Eq. (15) is identical to the well-known relationship, derived from both inhomogeneous [15,16,37,39] and homogeneous [41–43] solvation theories, which has been used to clarify the mechanism of protein

stability [15,37,38,44,45], hydrotropic solubilization [7–9,46] and food gelation [10,47,48]. (Note that the Gibbs-Duhem equation, $c_1V_1+c_2V_2=1$, was used in the final step of Eq. (15)). Eq. (15) can easily be solved by matrix inversion, since $\begin{vmatrix} 1 & -\frac{c_1}{c_2} \\ V_1 & V_2 \end{vmatrix} = \frac{1}{c_2} > 0$.

Thus we have formulated the preferential solvation theory in the framework of inhomogeneous solvation theory, shown the equivalence to the homogeneous solution theory approach [32–35,41–43], and demonstrated the ease by which different set of thermodynamic variables can be treated. The formalism presented here can straightforwardly be extended to the systems with concentrated solutes, by identifying one of the solvent species as solute [49].

## 3. Gibbs Adsorption isotherm

Here we generalize our theory to adsorption, and demonstrate that our inhomogeneous solvation theory approach enables an easy generalization to surface adsorption. We consider a system comprised of water and cosolvent molecules, forming vapour and liquid phases (denoted as I and II) that are in equilibrium. Generalization to $c$ component solutions in $p$ phases will be straightforward, but we focus here on the case of 2-components in 2-phases for the clarity in illustrating the general principles. According to Gibbs phase rule, the system has $F = 2 - 2 + 2 = 2$ degrees of freedom [16]. Under a constant temperature, the system has only one degree of freedom left.

Let us denote the grand partition functions of the liquid and vapour phases in isolation as $\Xi^I(T,V^I,\mu_1,\mu_2)$ and $\Xi^{II}(T,V^{II},\mu_1,\mu_2)$. We also consider these two systems facing each other in equilibrium, in the presence of the external field, still denoted as $u$, which in this case is a surface. The partition functions in the presence of the external field are denoted as $\Xi_u\left(T,V^I+V^{II},\mu_1,\mu_2\right)$. The total volume is kept constant at $V=V^I+V^{II}$. The free energy of the surface, $\gamma A$, where $\gamma$ is surface tension and $A$ is the surface area, can be expressed as

$$-\gamma A = -kT\ln\frac{\Xi_u(T,V^I+V^{II},\mu_1,\mu_2)}{\Xi_{\mathrm{u}}^I(T,V^I,\mu_1,\mu_2)\Xi_{\mathrm{u}}^{II}(T,V^{II},\mu_1,\mu_2)} \tag{16}$$

Eq. (16) thus demonstrates that generalization of preferential solvation (Eq. (2)) to multiple-phase systems is straightforward. Total differentiation of Eq. (16) under constant temperature yields

$$-Ad\gamma = [\langle N_1\rangle_u - \langle N_1\rangle^I - \langle N_1\rangle^{II}]d\mu_1 + [\langle N_2\rangle_u - \langle N_2\rangle^I - \langle N_2\rangle^{II}]d\mu_2 \tag{17}$$

which is also a straightforward generalization of Eq. (3), and is equivalent to the Gibbs adsorption isotherm [16]. Note that $\langle N_1\rangle_u - \langle N_1\rangle^I - \langle N_1\rangle^{II}$ and $\langle N_2\rangle_u - \langle N_2\rangle^I - \langle N_2\rangle^{II}$ represent the surface excesses of the species 1 and 2, respectively.

Having generalized the inhomogeneous preferential solvation theory to adsorption isotherm, let us see how matrix inversion plays a role in the independent determinability of excess numbers. Following our discussion in Section 2, one can construct the following simultaneous equations from Eq. (17):

$$-A\begin{pmatrix}\left(\frac{\partial\gamma}{\partial\mu_1}\right)_T\\ \left(\frac{\partial\gamma}{\partial\mu_2}\right)_T\end{pmatrix} = \begin{pmatrix}1 & \left(\frac{\partial\mu_2}{\partial\mu_1}\right)_T\\ \left(\frac{\partial\mu_1}{\partial\mu_2}\right)_T & 1\end{pmatrix}\begin{pmatrix}\langle N_1\rangle_u - \langle N_1\rangle^I - \langle N_1\rangle^{II}\\ \langle N_2\rangle_u - \langle N_2\rangle^I - \langle N_2\rangle^{II}\end{pmatrix} \tag{18}$$

The "stability condition" equivalent here is the following determinant, which can be proven easily to be

$$\begin{vmatrix} 1 & \left(\frac{\partial \mu_2}{\partial \mu_1}\right)_T \\ \left(\frac{\partial \mu_1}{\partial \mu_2}\right)_T & 1 \end{vmatrix} = 1 - \left(\frac{\partial \mu_1}{\partial \mu_2}\right)_T \left(\frac{\partial \mu_2}{\partial \mu_1}\right)_T = 0 \tag{19}$$

because of $\left(\frac{\partial \mu_1}{\partial \mu_2}\right)_T \left(\frac{\partial \mu_2}{\partial \mu_1}\right)_T = 1$, which can be justified by the fact that $T$ is the only other variable than $\mu_1$ and $\mu_2$ which has been allowed by the Gibbs phase rule. Because there is only one degree of freedom, there will only be one independent equation resulting from Eq. (18), which can be expressed as

$$-A\left(\frac{\partial \gamma}{\partial \mu_1}\right)_T = [\langle N_1 \rangle_u - \langle N_1 \rangle^I - \langle N_1 \rangle^{II}] + [\langle N_2 \rangle_u - \langle N_2 \rangle^I - \langle N_2 \rangle^{II}] \left(\frac{\partial \mu_2}{\partial \mu_1}\right)_T \tag{20}$$

Note that $\left(\frac{\partial \mu_2}{\partial \mu_1}\right)_T$ can be evaluated using the Gibbs-Duhem equations for the two bulk phases (I and II), which yields the Gibbs adsorption isotherm (see Appendix for derivation):

$$-Ad\gamma = \left[[\langle N_1 \rangle_u - \langle N_1 \rangle^I - \langle N_1 \rangle^{II}] - \left(\frac{c_1^I - c_1^{II}}{c_2^I - c_2^{II}}\right)[\langle N_2 \rangle_u - \langle N_2 \rangle^I - \langle N_2 \rangle^{II}]\right] d\mu_1 \tag{22}$$

where $c_i^\alpha$ represents the concentration (number density) of the species $i$ in phase $\alpha$.

Thus the inhomogeneous solvation theory approach to preferential solvation has been generalized to adsorption, in which the crucial role of the stability condition in the independent determinability of surface excesses have been clarified, regardless of the nature of the surface or external field, unlike our previous treatment of vapour-liquid surface [16]. The straightforwardness of generalization is due to the clarity upon which the surface excess can be defined in the inhomogeneous solvation approach.

## 4. Homogeneous versus inhomogeneous approaches to preferential solvation

So far in the present paper, we have completed the inhomogeneous solvation approach to fluctuation solution theory rigorously by generalizing earlier intuitive theory. We have demonstrated the equivalence to the homogeneous approach in the case of preferential solvation, as well as its advantage in the ease of generalizing the approach to adsorption isotherm. The fluctuation solution theory is now available in both perspectives with complementary strengths and advantages. Switching back and forth between the two perspectives will further facilitate the application to experimental systems especially when the choice of variables is not advantageous for one of the perspectives, as will be demonstrated in this section.

The key to converting an inhomogeneous solution to a homogeneous solution is to transform the external field, i.e., a solute fixed in its centre-of-mass position, into a freely moving molecule. This can be achieved by a well-known relationship by Gurney [50] and Ben-Naim [51] as

$$d\mu_u^* = d\mu_u - \frac{kT}{\langle N_u \rangle} d\langle N_u \rangle \tag{23}$$

Note that this procedure is known for solutes but not for surfaces.

We shall now demonstrate that the homogeneous-inhomogeneous conversion (Eq. (23)) plays a key role especially when the choice of the variables is not advantageous for inhomogeneous approach. For this purpose, let us study the following example:

**(v) Semi-permeable membrane transmitting everything but the biomolecule.** Let us focus here on a 3-component system in which many preferential solvation experiments have been performed. Since $\mu_1$ and $\mu_2$ are kept constant, Eq. (3) becomes

$$d\mu_u^* = -(\langle N_u \rangle_u - \langle N_u \rangle) d\mu_u \tag{24}$$

The problem with Eq. (24) is that it contains $\mu_u^*$ and $\mu_u$ at the same time. To get any useful information from Eq. (24) requires the use of Eq. (23) in conjunction, which yields

$$(1 + \langle N_u \rangle_u - \langle N_u \rangle) d\mu_u = \frac{kT}{\langle N_u \rangle} d\langle N_u \rangle \tag{25}$$

which is effectively a homogeneous relationship. (Note that $\langle N_u \rangle_u = \frac{\langle N_u (N_u - 1) \rangle}{\langle N_u \rangle}$ will convert Eq. (25) fully into a homogeneous relationship [39].) To render Eq. (25) useful in experimental data analysis, let us use the relationship straightforwardly obtainable from homogeneous grandcanonical ensemble, $kT \left( \frac{\partial \langle N_1 \rangle}{\partial \mu_u} \right)_{T,\mu_1\mu_2} = \langle N_u N_1 \rangle - \langle N_u \rangle \langle N_1 \rangle$ [39], which yields

$$\left( \frac{\partial \langle N_1 \rangle}{\partial \langle N_u \rangle} \right)_{T,\mu_1,\mu_2} = \frac{\langle N_u N_1 \rangle - \langle N_u \rangle \langle N_1 \rangle}{\langle N_u^2 \rangle - \langle N_u \rangle^2} \tag{26}$$

Eq. (26) is the number-based preferential hydration parameter which can be accessible by the use of the dialysis membrane [1]. Conversion of Eq. (26) to molarity or molality concentration scales will be straightforward [35]. Thus the inhomogeneous-homogeneous conversion (Eq. (23)) has facilitated the problem solving when the thermodynamic variables are not naturally suited for the inhomogeneous approach.

## 5. Conclusion

Preferential solvation [15,16] and adsorption isotherm [17–19] have been formulated on a unified and consistent theoretical framework based directly on grand partition functions in inhomogeneous

solvation theory [26–31,39]. We have shown that the phase stability condition is the basis for independent determination of excess numbers by enabling matrix inversion, which have been shown to be equivalent to the homogeneous solution theory. The major advantage of the inhomogeneous approach is its ease in generalizing preferential solvation theory to Gibbs adsorption isotherm, through which the origin of the analogy and difference between the two has been clarified via a unified matrix formulation. In addition, the total differentiation relationship of inhomogeneous solvation theory is particularly useful in formulating the matrix formulation that can be expressed in multiple ways adaptable to experimental conditions.

The theory presented here is a generalisation of the traditional approaches that go back to Wyman (thermodynamic linkage relationships) [52,53], to Casassa and Eisenberg (statistical thermodynamic theory of multicomponent solutions) [54], to Schellman and Tanford (solvent binding and exchange models) [55–58], Timasheff (concepts of preferential solvation) [1,12,14,23], and Parsegian (analogy between preferential solvation and adsorption) [13]. Here, the preferential solvation theory has been freed from the constraints of the binding models, and has been formulated in a way that its relationship to adsorption is clear. There is now a unified theory of solvent interactions with solutes and surfaces in the framework of inhomogeneous solvation theory, in which the phase stability condition clearly distinguishes a surface from a solute. In addition, the appropriate choice in the treatment of the solute (via homogeneous or inhomogeneous theories) together with their interconversion scheme will facilitate the theoretical treatment of solvation and adsorption in multiple component solutions.

**Acknowledgements**

This work was supported by the Gen Foundation, by the Grants-in-Aid for Scientific Research (Nos. 15K13550 and JP26240045) from the Japan Society for the Promotion of Science, by the Elements Strategy Initiative for Catalysts and Batteries and the Post-K Supercomputing Project from the Ministry of Education, Culture, Sports, Science, and Technology, and by the HPCI System Research Project (Project IDs: hp170097 and hp170221).

## Appendix

Derivation of Eq. (22) from Eq. (21) requires $\left(\frac{\partial \mu_2}{\partial \mu_1}\right)_T = -\left(\frac{c_1^I - c_1^{II}}{c_2^I - c_2^{II}}\right)$. This can be justified by the Gibbs-Duhem equations for the two bulk phases (I and II) under phase equilibrium ($\mu_i^I = \mu_i^{II} \equiv \mu_i$) and constant temperature

$$N_1^I d\mu_1 + N_2^I \mu_2 - V^I dP = 0 \quad \text{(A1)}$$

$$N_1^{II} d\mu_1 + N_2^{II} \mu_2 - V^{II} dP = 0 \quad \text{(A2)}$$

Eliminating $dP$ from Eqs. (A1) and (A2) yields

$$(c_1^I - c_1^{II}) d\mu_1 + (c_2^I - c_2^{II}) d\mu_2 = 0 \quad \text{(A3)}$$

where $c_i^I = N_i^I / V^I$ and $c_i^{II} = N_i^{II} / V^{II}$. Eq. (A3) easily leads to $\left(\frac{\partial \mu_2}{\partial \mu_1}\right)_T = -\left(\frac{c_1^I - c_1^{II}}{c_2^I - c_2^{II}}\right)$.

## References

[1] S.N. Timasheff, Control of protein stability and reactions by weakly interacting cosolvents:

the simplicity of the complicated., Adv. Protein Chem. 51 (1998) 355–432. doi:9615174.

[2] D. Harries, J. Rösgen, A practical guide on how osmolytes modulate macromolecular properties, Methods Cell Biol. 84 (2008) 679–735. doi:10.1016/S0091-679X(07)84022-2.

[3] V. Pierce, M. Kang, M. Aburi, S. Weerasinghe, P.E. Smith, Recent applications of Kirkwood–Buff theory to biological systems, Cell Biochem. Biophys. 50 (2008) 1–22. doi:10.1007/s12013-007-9005-0.

[4] P. Bauduin, A. Renoncourt, A. Kopf, D. Touraud, W. Kunz, Unified concept of solubilization in water by hydrotropes and cosolvents, Langmuir. 21 (2005) 6769–6775. doi:10.1021/la050554l.

[5] W. Kunz, K. Holmberg, T. Zemb, Hydrotropes, Curr. Opin. Colloid Interface Sci. 22 (2016) 99–107. doi:10.1016/j.cocis.2016.03.005.

[6] S. Schöttl, D. Horinek, Aggregation in detergent-free ternary mixtures with microemulsion-like properties, Curr. Opin. Colloid Interface Sci. 22 (2016) 8–13. doi:10.1016/j.cocis.2016.02.003.

[7] J.J. Booth, S. Abbott, S. Shimizu, Mechanism of hydrophobic drug solubilization by small molecule hydrotropes, J. Phys. Chem. B. 116 (2012) 14915–14921. doi:10.1021/jp309819r.

[8] S. Shimizu, J.J. Booth, S. Abbott, Hydrotropy: binding models vs. statistical thermodynamics., Phys. Chem. Chem. Phys. 15 (2013) 20625–20632. doi:10.1039/c3cp53791a.

[9] J.J. Booth, M. Omar, S. Abbott, S. Shimizu, Hydrotrope accumulation around the drug: the driving force for solubilization and minimum hydrotrope concentration for nicotinamide and urea, Phys Chem Chem Phys. 17 (2015) 8028–8037. doi:10.1039/C4CP05414H.

[10] S. Shimizu, R. Stenner, N. Matubayasi, Gastrophysics: Statistical thermodynamics of

biomolecular denaturation and gelation from the Kirkwood-Buff theory towards the understanding of tofu, Food Hydrocoll. 62 (2017) 128–139. doi:10.1016/j.foodhyd.2016.07.022.

[11] S. Shimizu, N. Matubayasi, Unifying hydrotropy under Gibbs phase rule, Phys. Chem. Chem. Phys. 19 (2017) 23597–23605.

[12] S.N. Timasheff, In disperse solution, "osmotic stress" is a restricted case of preferential interactions, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 7363–7367. doi:10.1073/pnas.95.13.7363.

[13] V.A. Parsegian, R.P. Rand, D.C. Rau, Osmotic stress, crowding, preferential hydration, and binding: A comparison of perspectives., Proc. Natl. Acad. Sci. U. S. A. 97 (2000) 3987–3992. doi:10.1073/pnas.97.8.3987.

[14] S.N. Timasheff, Protein hydration, thermodynamic binding, and preferential hydration, Biochemistry. 41 (2002) 13473–13482. doi:10.1021/bi020316e.

[15] S. Shimizu, Estimating hydration changes upon biomolecular reactions from osmotic stress, high pressure, and preferential hydration experiments., Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 1195–1199. doi:10.1073/pnas.0305836101.

[16] S. Shimizu, N. Matubayasi, Preferential solvation: Dividing surface vs excess numbers, J. Phys. Chem. B. 118 (2014) 3922–3930. doi:10.1021/jp410567c.

[17] J.W. Gibbs, The collected works of J. W. Gibbs, Yale University Press, New Haven, CT, 1928.

[18] R. Defay, I. Prigogine, Surface tension and adsorption, Longmans, London, 1966.

[19] B. Widom, Remarks on the Gibbs adsorption equation and the van der Waals, Cahn-Hilliard theory of interfaces, Physica A. 95 (1979) 1–11. doi:10.1016/0378-4371(79)90041-4.

[20] E.A. Ploetz, P.E. Smith, Local fluctuations in solution mixtures, J. Chem. Phys. 135 (2011) 44506. doi:10.1063/1.3615718.

[21] F. Chen, P.E. Smith, Theory and computer simulation of solute effects on the surface tension of liquids, J. Phys. Chem. B. 112 (2008) 8975–8984. doi:10.1021/jp711062a.

[22] B. Widom, New views of the Gibbs adsorption equation, Physica A. 372 (2006) 169–172. doi:10.1016/j.physa.2006.08.007.

[23] S.N. Timasheff, Protein-solvent preferential interactions, protein hydration, and the modulation of biochemical reactions by solvent components., Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 9721–6. doi:10.1073/pnas.122225399.

[24] S. Shimizu, N. Matubayasi, Osmolyte depletion viewed in terms of the dividing membrane and its work of expansion against osmotic pressure, Biophys. Chem. (2017) DOI: 10.1016/j.bpc.2017.02.003. doi:10.1016/j.bpc.2017.02.003.

[25] I. Prigogine, R. Defay, Chemical Thermodynamics, Longmans, London, 1954.

[26] J.K. Percus, Approximation methods in classical statistical mechanics, Phys. Rev. Lett. 8 (1962) 462–463. doi:10.1103/PhysRevLett.8.462.

[27] D. Henderson, Fundamentals of inhomogeneous fluids, Marcel Dekker, New York, 1992.

[28] J.-P. Hansen, I.R. McDonald, Theory of simple liquids: with applications to soft matter, Academic Press, Amsterdam, 2013.

[29] T. Lazaridis, Inhomogeneous fluid approach to solvation thermodynamics. 1. Theory, J. Phys. Chem. B. 102 (1998) 3531–3541. doi:10.1021/jp9723574.

[30] T. Lazaridis, Inhomogeneous fluid approach to solvation thermodynamics. 2. Applications to simple fluids, J. Phys. Chem. B. 102 (1998) 3542–3550. doi:10.1021/jp972358w.

[31] R.M. Levy, D. Cui, B.W. Zhang, N. Matubayasi, Relationship between solvation

thermodynamics from IST and DFT perspectives, J. Phys. Chem. B. 121 (2017) 3825–3841. doi:10.1021/acs.jpcb.6b12889.

[32] J.G. Kirkwood, F.P. Buff, The statistical mechanical theory of solutions. I, J. Chem. Phys. 19 (1951) 774–777. doi:10.1063/1.1748352.

[33] A. Ben-Naim, Inversion of the Kirkwood–Buff theory of solutions: Application to the water–ethanol system, J. Chem. Phys. 67 (1977) 4884–4890. doi:10.1063/1.434669.

[34] P.E. Smith, On the Kirkwood-Buff inversion procedure, J. Chem. Phys. 129 (2008) 124509.

[35] M. Kang, P.E. Smith, Kirkwood–Buff theory of four and higher component mixtures, J. Chem. Phys. 128 (2008) 244511. doi:10.1063/1.2943318.

[36] D.G. Hall, Kirkwood-Buff theory of solutions. An alternative derivation of part of it and some applications, Trans. Faraday Soc. 67 (1971) 2516–2524. doi:10.1039/tf9716702516.

[37] S. Shimizu, C.L. Boon, The Kirkwood-Buff theory and the effect of cosolvents on biochemical reactions, J. Chem. Phys. 121 (2004) 9147–9155. doi:10.1063/1.1806402.

[38] S. Shimizu, W.M. McLaren, N. Matubayasi, The Hofmeister series and protein-salt interactions, J. Chem. Phys. 124 (2006) 234905. doi:10.1063/1.2206174.

[39] S. Shimizu, N. Matubayasi, Hydrotropy: Monomer-micelle equilibrium and minimum hydrotrope concentration, J. Phys. Chem. B. 118 (2014) 10515–10524. doi:10.1021/jp505869m.

[40] S. Shimizu, H.S. Chan, Statistical mechanics of solvophobic aggregation: Additive and cooperative effects, J. Chem. Phys. 115 (2001) 3424–3431. doi:10.1063/1.1386420.

[41] P.E. Smith, Cosolvent interactions with biomolecules: Relating computer simulation data to experimental thermodynamic data, J. Phys. Chem. B. 108 (2004) 18716–18724. doi:10.1021/jp0474879.

[42] P.E. Smith, Equilibrium dialysis data and the relationships between preferential interaction parameters for biological systems in terms of kirkwood-buff integrals, J. Phys. Chem. B. 110 (2006) 2862–2868. doi:10.1021/jp056100e.

[43] P.E. Smith, Chemical potential derivatives and preferential interaction parameters in biological systems from Kirkwood-Buff theory, Biophys. J. 91 (2006) 849–856. doi:10.1529/biophysj.105.078790.

[44] S. Shimizu, N. Matubayasi, Preferential hydration of proteins: A Kirkwood-Buff approach, Chem. Phys. Lett. 420 (2006) 518–522. doi:10.1016/j.cplett.2006.01.034.

[45] S. Shimizu, Molecular origin of the cosolvent-induced changes in the thermal stability of proteins, Chem. Phys. Lett. 514 (2011) 156–158. doi:10.1016/j.cplett.2011.08.038.

[46] S. Abbott, J.J. Booth, S. Shimizu, Practical molecular thermodynamics for greener solution chemistry, Green Chem. 19 (2017) 68–75. doi:10.1039/C6GC03002E.

[47] S. Shimizu, N. Matubayasi, Gelation: The role of sugars and polyols on gelatin and agarose, J. Phys. Chem. B. 118 (2014) 13210–13216. doi:10.1021/jp509099h.

[48] R. Stenner, N. Matubayasi, S. Shimizu, Gelation of carrageenan: Effects of sugars and polyols, Food Hydrocoll. 54 (2016) 284–292. doi:10.1016/j.foodhyd.2015.10.007.

[49] J.E.S.J. Reid, A.J. Walker, S. Shimizu, Residual water in ionic liquids: clustered or dissociated?, Phys. Chem. Chem. Phys. 17 (2015) 14710–14718. doi:10.1039/c5cp01854d.

[50] R.W. Gurney, Ionic processes in solution, McGraw-Hill, New York, 1953.

[51] A. Ben-Naim, Standard thermodynamics of transfer. Uses and misuses, J. Phys. Chem. 82 (1978) 792–803. doi:10.1021/j100496a008.

[52] J. Wyman, Heme proteins, Adv. Protein Chem. 4 (1948) 407–531. doi:10.1016/S0065-3233(08)60011-X.

[53] J. Wyman, Linked functions and reciprocal effects in hemoglobin: A second look, Adv. Protein Chem. 19 (1964) 223–286. doi:10.1016/S0065-3233(08)60190-4.

[54] E.F. Casassa, H. Eisenberg, Thermodynamic analysis of multicomponent solutions, Adv. Protein Chem. 19 (1964) 287–395. doi:10.1016/S0065-3233(08)60191-6.

[55] C. Tanford, Protein denaturation, Adv. Protein Chem. 23 (1968) 121–282. doi:10.1021/la200704s.

[56] C. Tanford, Protein denaturation. Part C. Theoretical models for the mechanism of denaturation, Adv. Protein Chem. 24 (1970) 1–95. doi:10.1016/S0065-3233(08)60241-7.

[57] J.A. Schellman, Solvent denaturation, Biopolymers. 17 (1978) 1305–1322. doi:10.1002/bip.1978.360170515.

[58] J.A. Schellman, Selective binding and solvent denaturation, Biopolymers. 26 (1987) 549–559. doi:10.1002/bip.360260408.